

Appendix A

PROCESS FOR MAKING BOC-PROTECTED 3-
AMINOHYDANTOINS/THIOHYDANTOINS AND 3-
AMINODIHYDROURACILS/DIHYDROTHIOURACILS

This application is a 371 of PCT/US00/27503 filed October 5, 2000 which claims the benefit of Provisional Application No. 60/158,660 filed October 8, 1999.

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Technical Field

The present invention is directed to a process for the efficient solution and solid-phase synthesis of Boc-protected 3-aminohydantoins/thiohydantoins and 3-aminodihydrouracils/dihydrothiouracils.

Background of the Invention

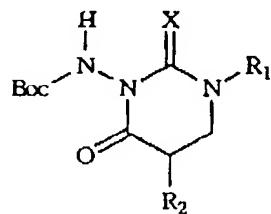
10 The present invention is directed to a novel process for synthesizing Boc-protected 3-aminohydantoins, 3-aminodihydrouracils, and their thio-substituted counterparts using a one-pot solution-phase or solid-phase process. 3-aminohydantoin and 3-aminodihydrouracil derivatives are useful in both the pharmaceutical and agrochemical industries. For example, compounds containing the 3-aminohydantoin or
15 3-aminodihydrouracil nucleus are useful as anticonvulsant agents, antibacterial agents, metalloprotease inhibitors, diuretic agents, and pesticides.

Synthetic routes for the preparation of 3-aminohydantoin derivatives are disclosed in the following references: Kiec-Kononowicz, K.; Zejc, A.; Byrtus, H. *Pol. J. Chem.* 1984, 58, 585. Lange, J. et al. *Polish Patent*, PL 123138 B1, April 30, 1984. Wright, G. C.; Michels, J. G.; Spencer, C. F. *J. Med. Chem.* 1969, 12, 379-381. Bernard, L. et al. *French Patent*, 2000801, January 24, 1969. Kobayashi, N. et al. *Japanese Patent*, 09176131 A2, July 8, 1997. Taub, W. *U.S. Patent* 2767193, 1956. *Chem. Abstr.*, 1957, 51, 5811. Szczepanski, H.; Kristinsson, H.; Maienfish, P.; Ehrenfreund, J. *WO 95/18123*, 1995. Lindemann, A.; Khan, N. H.; Hofmann, K. *J. Am. Chem. Soc.*, 1952, 74, 476-479.
20 Gante, J.; Lautsch, W. *Chem. Ber.*, 1964, 97, 994. Schlogl, K.; Derkosch, J.; Korger, G. C. *Monatsh. Chem.* 1954, 85, 607. Schlogl, K.; Korger, G. *Monatsh. Chem.* 1951, 82, 799. Davidson, J. S. *J. Chem. Soc.* 1964, 4646-4647. Gillis, B. T.; Dain, J. G. *J. Heterocyclic Chem.* 1971, 8, 339-339. Wildonger, R. A.; Winstead, M. B. *J. Heterocyclic Chem.* 1967, 4, 981-982. Lalezari, I. *J. Heterocyclic Chem.* 1985, 22, 741-743. Saegusa, Y.; Harada, S.; Nakamura, S. *J. Heterocyclic Chem.* 1990, 27, 739-742. Milcent, R.; Akhnazarian, A.; Lensen, N. *J. Heterocyclic Chem.* 1996, 33, 1829-1833. Ragab, F. A.; Eid, N. M.; El-Tawab, H. A. *Pharmazie* 1997, 52 (12), 926-929. Yoon, J; Cho, C-W; Han, H; Janda, K. D. *Chem. Comm.* 1998, 2703-2704. However, in general the synthetic routes disclosed above involve multiple steps, require harsh reaction conditions, and/or produce relatively low yields.

14. (Currently Amended)

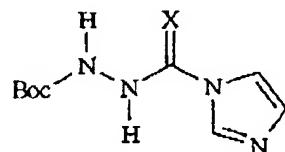
A method for making a 3-aminodihydrouracil or 3-

aminodihydrothiouracil having the formula:

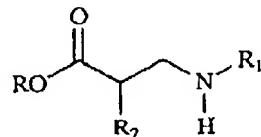


wherein X is oxygen or sulfur, R₁ is hydrogen, alkyl, a heterocyclic ring, an aromatic ring, or a heteroaromatic ring; R₂ is hydrogen, alkyl, a heterocyclic ring, an aromatic ring, or a heteroaromatic ring; or R₁ and the member carbon atom adjacent to the carbon atom containing R₂ can be taken together to form a ring system; said ring system being carboxylic carbocyclic ring, heterocyclic ring or heteroaromatic ring; said method comprising the steps of:

a) reacting a hydrazine compound having the formula:



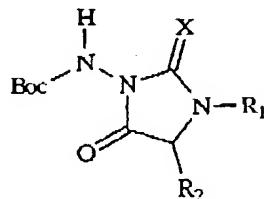
with an amino acid ester having the formula:



R is alkyl, carbocyclic ring, heterocyclic ring, aromatic ring, or heteroaromatic ring, to form a reaction mixture; and

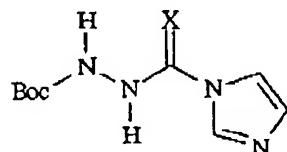
b) heating said reaction mixture to form said 3-aminodihydrouracil or 3-aminodihydrothiouracil.

26. (Currently amended) A method for making a hydantoin or thiohydantoin having the formula:

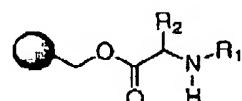


wherein X is oxygen or sulfur, R₁ is hydrogen, alkyl, a heterocyclic ring, an aromatic ring, or a heteroaromatic ring; R₂ is hydrogen, alkyl, a heterocyclic ring, an aromatic ring, or a heteroaromatic ring; or R₁ and R₂ can be taken together to form a fused carbocyclic ring, heterocyclic ring, a fused aromatic ring, or a fused heteroaromatic ring with the hydantoin or thiohydantoin ring; said method comprising the steps of:

a) reacting a hydrazine compound having the formula:



with a resin-bound amino acid ester having the formula:



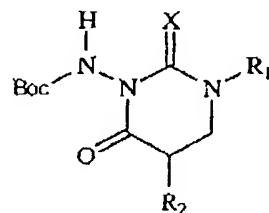
wherein the symbol:



signifies a Merrifield resin, hydroxymethyl resin, Wang resin, or PEG resin; to form a reaction mixture; and

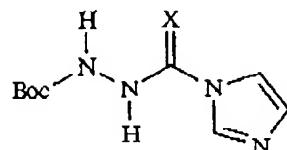
b) heating said reaction mixture to form said hydantoin or thiohydantoin.

27. (Currently Amended) A method for making a 3-aminodihydrouracil or 3-aminodihydrothiouracil having the formula:

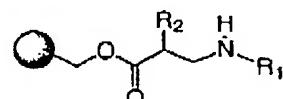


wherin X is oxygen or sulfur, R₁ is hydrogen, alkyl, a heterocyclic ring, an aromatic ring, or a heteroaromatic ring; R₂ is hydrogen, alkyl, a heterocyclic ring, an aromatic ring, or a heteroaromatic ring; or R₁ and the member carbon atom adjacent to the carbon atom containing R₂ can be taken together to form a fused carbocyclic ring, heterocyclic ring, a fused aromatic ring, or a fused heteroaromatic ring with the 3-aminodihydrouracil or 3-aminodihydrothiouracil ring; said method comprising the steps of:

a) reacting a hydrazine compound having the formula:



with an amino acid ester having the formula:



wherein the symbol:



signifies a Merrifield resin, hydroxymethyl resin, Wang resin, or PEG resin; to form a reaction mixture; and

b) heating said reaction mixture to form said 3-aminodihydrouracil or 3-aminodihydrothiouracil.